THE BULLETIN OF Mathematical BIOPHYSICS

JUNE 1945

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THE UNIVERSITY OF CHICAGO PRESS · CHICAGO · ILLINOIS

VOLUME 7 · · · · · NUMBER 2

THE BULLETIN OF MATHEMATICAL BIOPHYSICS

EDITED BY N. RASHEVSKY

The Bulletin is devoted to publications of research in Mathematical Biophysics, as described on the inside back cover.

THE BULLETIN is published by the University of Chicago at the University of Chicago Press, 5750 Ellis Avenue, Chicago, Illinois, quarterly, in March, June, September, December. ¶The subscription price is $2.50 per year, the price of single copies is 75 cents. Orders for service of less than a full year will be charged at the single-copy rate. ¶Patrons are requested to make all remittances payable to The University of Chicago Press in postal or express money orders or bank drafts.

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BUSINESS CORRESPONDENCE should be addressed to The University of Chicago Press, Chicago, Ill.

COMMUNICATIONS FOR THE EDITOR and manuscripts should be addressed to N. Rashevsky, Editorial Office of the Bulletin of Mathematical Biophysics, 5822 Drexel Avenue, Chicago, Ill.

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PRINTED BY THE DENTAN PRINTING COMPANY · · · COLORADO SPRINGS, COLORADO

BULLETIN OF
MATHEMATICAL BIOPHYSICS
VOLUME 7, 1945

A NOTE ON THE PHYSIOLOGICAL ARRANGEMENT OF TISSUES

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Presented are the kinetics of uptake of an inert solute by tissues arranged in series, distinct parallel and competitive parallel, with respect to the circulation. The uptake in all cases can be described by a series of exponentials, but the number of these terms and the character of the constants is specific for each arrangement. This fact can be of value in deducing tissue arrangement from uptake data.

In the course of studying the inert gas exchanges of tissues (Smith and Morales, 1944a, b, c), we were confronted with the problem of deciding on some type of arrangement of tissues with respect to the circulation. Experience taught us that this was not always an obvious choice, and that anatomical considerations could not always be counted upon to give a categorical answer. We were thus prompted to study the matter in more detail, and eventually were led to the considerations given below. The terminology and postulates are those suited to the metabolism of a chemically inert substance, but it is clear that the general principle is extensible to other kinds of substances.

The three fundamental arrangements which we believe actually occur in nature are depicted in Figure 1. Assuming that the blood flow is constant, and that the solute in question permeates barriers at a rate proportional to the concentration difference across the barriers, we may readily obtain the kinetic equations for each arrangement by applying the simple condition of material balance.

We shall use the following notations in which the subscript i refers to the i-th tissue:

R—rate of blood flow ($cm^3\ sec^{-1}$),
C—arterial delivery concentration ($gm\ cm^{-3}$),
x_i^0—average solute concentration of blood in exchange with the i-th tissue,

* The material in this article is the opinion of the writers, and should not be construed as representing the policies of the Navy Department or the Naval Service at large.

V_i^0—volume of blood chamber exchanging with the i-th tissue,
x_i—average concentration (gm cm^{-3}),
h_i—permeability (cm sec^{-1}),
S_i—exchange surface (cm^2),
V_i—volume (cm^3),
α_i—solubility in plasma/solubility in i-th tissue,
π_i—$\alpha_i h_i S_i / V_i$.

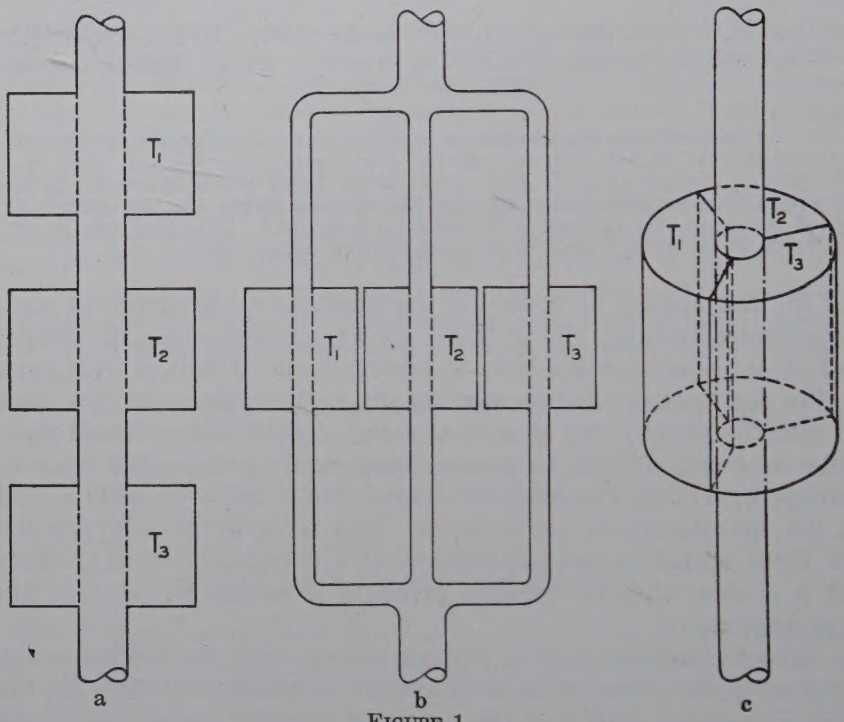

FIGURE 1

I. Series Arrangement (Figure 1a). Applying the material balance condition to the blood chamber and tissue respectively, we obtain

$$V_i^0 dx_i^0/dt = R(x_{i-1}^0 - x_i^0) - h_i S_i (x_i^0 - \alpha_i x_i), \tag{1}$$

$$V_i dx_i/dt = h_i S_i (x_i^0 - \alpha_i x_i), \quad i = 1, 2, \cdots, n; \quad x_0^0 = C. \tag{2}$$

Eliminating x_i between equations (1) and (2), we have

$$V_i^0 \frac{d^2 x_i^0}{dt^2} + \left[R + \pi_i \left(V_i^0 + \frac{V_i}{\alpha_i} \right) \right] \frac{dx_i^0}{dt} + R\pi_i x_i^0 = R \frac{dx_{i-1}^0}{dt} + R\pi_i x_{i-1}^0 = f_i(t). \tag{3}$$

Denoting the two roots of the auxiliary equation (both of which can be shown to be negative) by $-k_{i1}$ and $-k_{i2}$, we may write the solution of equation (3) as

$$x_i^0 = \frac{e^{-k_{i,1}t} \int e^{k_{i,1}t} f_i(t)\, dt - e^{-k_{i,2}t} \int e^{k_{i,2}t} f_i(t)\, dt}{k_{i,2} - k_{i,1}} + B_{i,1}^{(i)}\, e^{-k_{i,1}t} + B_{i,2}^{(i)}\, e^{-k_{i,2}t}, \tag{4}$$

where the B's are constants of integration. Now when $i = 1$,

$$x_1^0 = C + B_{1,1}^{(1)}\, e^{-k_{1,1}t} + B_{1,2}^{(1)}\, e^{-k_{1,2}t}.$$

Furthermore, if it is assumed that

$$x_i^0 = C + \sum_{s=1}^{s=i} (B_{i,1}^{(s)}\, e^{-k_{s,1}t} + B_{i,2}^{(s)}\, e^{-k_{s,2}t}), \tag{5}$$

then it can be shown that

$$x_{i+1}^0 = C + \sum_{s=1}^{s=i+1} (B_{i+1,1}^{(s)}\, e^{-k_{s,1}t} + B_{i+1,2}^{(s)}\, e^{-k_{s,2}t}). \tag{6}$$

Since these are the two conditions for an induction, we can conclude that equation (5) is the correct solution of the system (1) and (2). Adding equations (1) and (2), and rearranging, we have

$$V_i x_i + V_i^0 x_i^0 = \text{Constant} - R \int (x_i^0 - x_{i-1}^0)\, dt. \tag{7}$$

Since $\sum_{i=1}^{i=n} V_i x_i + V_i^0 x_i^0 = \Phi(t)$, we have on summating expression (7) over i,

$$\Phi(t) = \Phi(\infty) + R \int (x_i^0 - x_n^0)\, dt = \Phi(\infty) - \sum_{s=1}^{s=n} (Q_{s,1}\, e^{-k_{s,1}t} + Q_{s,2}\, e^{-k_{s,2}t}). \tag{8}$$

II. Distinct Parallel Arrangement (Figure 1b). In this case the equations of material balance are identical with equations (1) and (2), except that x_{i-1}^0 is every where replaced by C. Therefore, using the same methods as in the preceding section, we may write immediately

$$\Phi(t) = \Phi(\infty) - \sum_{i=1}^{i=n} (A_{i,1}\, e^{-k_{i,1}t} + A_{i,2}\, e^{-k_{i,2}t}), \tag{9}$$

noting, however, the important difference that the coefficients as well as the decay constants are determined solely by the parameters of the i-th tissue.

III. Competitive Parallel Arrangement (Figure 1c). This case is somewhat more involved. A complete solution together with a discussion of its properties is given elsewhere (Smith and Morales, 1944a). Here we only cite the final result,

$$\Phi(t) = \Phi(\infty) - \sum_{j=0}^{j=n} Q_j\, e^{-k_j t}, \qquad (10)$$

wherein both Q's and k's are composite constants, involving the parameters of all tissues.

Equations (8), (9), and (10) express certain generalizations which have important experimental relevance. These are best set forth in tabular form, as shown in Table I.

TABLE I

TISSUE ARRANGEMENT	TYPE OF FUNCTION DESCRIBING	NO. OF EXPNTLS.	CONSTANT COEFFS.	DECAY CONSTANTS
Series	Expntl. Sum	$2n$*	Refer to all tissues	Each determined by only one tissue
Distinct Parallel	Expntl. Sum	$2n$	Each determined by one tissue	Each determined by only one tissue
Competitive Parallel	Expntl. Sum	$n + 1$	Refer to all tissues	Refer to all tissues

* n = number of tissues.

The universality of the exponential sum in describing these processes is of course a mathematical consequence of the ordinary linear differential equation which is assumed to govern the penetration of a barrier by inert solutes. A technical corollary following on the adoption of exponential expressions is the fact that experimental data on linear penetrations will simplify when plotted semi-logarithmically.

The number of exponentials which empirically can be found to satisfy the data is a very good index of the type of tissue or absorbing element arrangement. In our limited experience (Smith and Morales, 1944c) we have found that gross mammalian tissue regions are usually of the competitive parallel type, but doubtless the gradients along circulatory portal systems and along individual blood vessels coursing through one tissue (see Bloch, 1941) are of the series type, and such regions as fat depots are certainly of the distinct parallel type.

The degree of coupling in the various systems is reflected in the nature of the constants, both coefficient and decay. Failure to recognize this interdependence leads to much confusion in the interpretation of data.

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BULLETIN OF
MATHEMATICAL BIOPHYSICS
VOLUME 7, 1945

DYNAMICS OF QUADRUPEDAL LOCOMOTION

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O. Fischer's dynamical equations for unbranched systems in two dimensions are extended to the branched systems exhibited by a quadruped.

O. Fischer (1906) has worked out the mathematical theory of an unbranched system of linked levers, and has indicated briefly how the theory can be extended to branched systems. Fischer's developments, elaborated in a long series of contributions, dealt principally with the dynamical constants of the individual members of the body (especially the human body) and the mechanics of their movements as the body remains fixed.

N. Rashevsky (1944) has discussed the effect of the form of the organism upon the energetics of locomotion, considering principally the rhythmic raising and lowering of the center of gravity with each step. The work done in raising the center of gravity is of course not recovered by the organism in the subsequent lowering. There are numerous other ways in which energy is lost to the organism during locomotion. Surface friction and wind resistance will vary with the external circumstances. Internal friction and viscosity are properties of the organism, and A. V. Hill (1926) regarded the viscous losses as quite high, though W. O. Fenn (1938) considers them to be much smaller if not entirely negligible. The efficiency of the muscular machinery, high as it is, is still limited, and is, moreover, a function of the speed of doing the work, being low for both high speeds and low speeds. Finally, a consideration closely related to that of the efficiency, the possible modulating effects of antagonistic effectors will require the expenditure of energy when and if these occur. Thus, according to W. O. Fenn (1938), in swinging the arm rapidly back and forth, before the swing is completed in one direction those muscles have already become active which will terminate the swing and reverse its direction. Hence, although mechanically the arm is performing work upon these muscles before the swing has reversed itself, physiologically the muscles are in a state of activity and energy is being lost to the system in the form of heat. Such events may occur during locomotion.

Whether or not the modulating effects occur to any appreciable extent, the variation of efficiency with speed is considerable, so that the speed of locomotion is limited in two ways at least: as regards the rate at which energy can be supplied, and the rate at which it can be efficiently utilized. But again, the relation between the rate of locomotion and the rate of shortening of the muscles depends in large measure upon the bodily structure. It seems desirable therefore to apply O. Fischer's methods to the case of the branched system formed by the usual quadruped consisting of a trunk and four extremities, the head being, for the present, neglected, or rather, regarded as rigidly attached to the trunk.

At first we consider only the oversimplified case of rigid extremities. We follow in general the notations of O. Fischer. The subscripts 0 will denote the trunk, 1 the left and 2 the right foreleg, 3 the left and 4 the right hind leg. The subscripted letters S denote the centroids of the five members and the subscripted letters H denote the "reduced centroids" of O. Fischer, to be defined presently. We denote the extremities of the legs (the "feet") by $A_i (i = 1, 2, 3, 4)$, while B^1 denotes the point of attachment of the forelegs, B^2, that of the hind legs, to the trunk. The five members are supposed constrained to a vertical plane, the sole movement of a leg relative to the trunk being that of a rotation about a horizontal axis through the point B^1 or B^2 as the case may be. The centroid of the system we denote by S without a subscript. Vectors to the various points drawn from an arbitrary fixed origin we denote by small letters in boldface, and in general, a small letter boldfaced will represent a vector, and the same letter in ordinary type the length of this vector.

Distances along the animal will be measured from B^2 in either direction, the signs being so adjusted.

Now, m being the mass of the system,

$$\begin{aligned} m\boldsymbol{s} &= \sum_0^4 m_i \boldsymbol{s}_i , \\ m\boldsymbol{h}_0 &= m_0\boldsymbol{s}_0 + (m_1 + m_2)\boldsymbol{b}^{(1)} + (m_3 + m_4)\boldsymbol{b}^{(2)}, \end{aligned} \tag{1}$$

when H_0 is the centroid of the system consisting of the trunk, with the masses of the two forelegs concentrated at B^1 and those of the two hind legs concentrated at B^2. Similarly H_1 is the centroid of the system consisting of the left foreleg with the masses of the trunk and the other three legs concentrated at B^1, whence

$$m\boldsymbol{h}_1 = m_1\boldsymbol{s}_1 + (m_0 + m_2 + m_3 + m_4)\boldsymbol{b}^{(1)}. \tag{2}$$

The other H_i and $\boldsymbol{h}_i$ are determined in an analogous way. Hence

$$\sum \boldsymbol{h}_i = \boldsymbol{s} + 2\boldsymbol{b}^{(1)} + 2\boldsymbol{b}^{(2)}, \tag{3}$$

so that

$$\begin{aligned} \boldsymbol{s} &= \boldsymbol{h}_0 + (\boldsymbol{h}_1 - \boldsymbol{b}^{(1)}) + (\boldsymbol{h}_2 - \boldsymbol{b}^{(1)}) + (\boldsymbol{h}_3 - \boldsymbol{b}^{(2)}) + (\boldsymbol{h}_4 - \boldsymbol{b}^{(2)}) \\ &= (\boldsymbol{h}_0 - \boldsymbol{b}^{(1)}) + \boldsymbol{h}_1 + (\boldsymbol{h}_2 - \boldsymbol{b}^{(1)}) + (\boldsymbol{h}_3 - \boldsymbol{b}^{(2)}) + (\boldsymbol{h}_4 - \boldsymbol{b}^{(2)}) \\ &= \cdots . \end{aligned} \tag{4}$$

The centroid S is thus determined by the various H_i in a manner wholly analogous to its determination in the case of an unbranched system, as, indeed, O. Fischer (1906) has shown.

The kinetic energy of the system can be calculated much as O. Fischer has done for an unbranched system. We employ hereafter the following indices according to the range:

$$\begin{aligned} &\nu = 1, 2; \qquad i, j, k = 1, 2, 3, 4; \\ &\rho, \sigma = 0, 1, 2, 3, 4 . \end{aligned}$$

Define

$$\begin{aligned} q^{(\nu)} &= \overline{B^\nu S_0}, \\ q_i = \overline{B^\nu S_i}, &\qquad p_i = \overline{S_i A_i}, \\ e_\rho = \overline{H_\rho S_\rho}, &\qquad c^{(\nu)} = \overline{B^\nu H_0}, \\ c_i = \overline{B^\nu H_i}, &\qquad d_i = \overline{H_i A_i}, \end{aligned} \tag{5}$$

understanding that in defining q_i and c_i, $\nu = 1$ when $i = 1$ or 2, $\nu = 2$ when $i = 3$ or 4. Note that according to our sign-convention $q^{(1)} < 0$, $c^{(1)} < 0$, e_0 may be positive or negative according to the case, and all other quantities are positive.

It follows now that

$$\begin{aligned} q_i &= c_i + e_i, \qquad & p_i &= d_i - e_i, \\ & q^{(\nu)} = c^{(\nu)} + e_0 . \end{aligned} \tag{6}$$

Let θ_ρ represent the inclination with the horizontal of the ρ-th member. The system is then completely determined when the position vector $\boldsymbol{s}$ and the five angles θ_ρ are specified. We now calculate the translations $d\boldsymbol{s}_\rho$ undergone by S_ρ as a result of a small rotation $d\theta_\rho$ of one member, the centroid S and the remaining θ's being held fixed. In this operation H_σ remains fixed, S_ρ rotates about H_σ, and all other S_ρ describe circular arcs congruent to those described by the B^ν. Therefore, if we let x_ρ, y_ρ represent the coordinates of the S_ρ, and combine the results of the five rotations, we have

$$
\begin{aligned}
dx_0 &= -\,e_0 \sin\theta_0\, d\theta_0 - \sum c_i \sin\theta_i\, d\theta_i\,, \\
dy_0 &= +\,e_0 \cos\theta_0\, d\theta_0 + \sum c_i \cos\theta_i\, d\theta_i\,, \\
dx_h &= q_h \sin\theta_h\, d\theta_h + c^{(1)} \sin\theta_0\, d\theta_0 - \sum c_j \sin\theta_j\, d\theta_j\,, \qquad (h=1,2) \\
dy_h &= -q_h \cos\theta_h\, d\theta_h - c^{(1)} \cos\theta_0\, d\theta_0 + \sum c_j \cos\theta_j\, d\theta_j\,, \qquad (7) \\
dx_h &= q_h \sin\theta_h\, d\theta_h + c^{(2)} \sin\theta_0\, d\theta_0 - \sum c_j \sin\theta_j\, d\theta_j\,, \qquad (h=3,4) \\
dy_h &= -q_h \cos\theta_h\, d\theta_h - c^{(2)} \cos\theta_0\, d\theta_0 + \sum c_j \cos\theta_j\, d\theta_j\,.
\end{aligned}
$$

If we add in the kinetic energy of rotation of each member about its centroid, we obtain from these equations the total kinetic energy of rotation,

$$
\begin{aligned}
T_r = \tfrac{1}{2}m\{&\sum \lambda_\rho^2\, \dot\theta_\rho^2 + 2\sum c^{(\nu)}\, c_i \cos(\theta_i - \theta_0)\, \dot\theta_0\, \dot\theta_i \\
&- 2\sum_{i\neq j}\sum c_i\, c_j \cos(\theta_i - \theta_j)\, \dot\theta_i\, \dot\theta_j\}\,,
\end{aligned} \qquad (8)
$$

where λ_ρ is the radius of gyration of the reduced system about H_ρ, and the index $\nu = 1$ when $i = 1, 2$, and $\nu = 2$ when $i = 3, 4$. The total kinetic energy is therefore

$$
\begin{aligned}
T = \tfrac{1}{2}m\{&\dot x^2 + \dot y^2 + \sum \lambda_\rho^2\, \dot\theta_\rho^2 + 2\sum c^{(\nu)}\, c_i \cos(\theta_i - \theta_0)\, \dot\theta_i\, \dot\theta_j \\
&- 2\sum_{i\neq j}\sum c_i\, c_j \cos(\theta_i - \theta_j)\, \dot\theta_i\, \dot\theta_j\}\,.
\end{aligned} \qquad (9)
$$

If we write

$$
(f_{\rho\sigma}) = \begin{pmatrix}
\lambda_0^2 & c^{(1)}c_1 & c^{(1)}c_2 & c^{(2)}c_3 & c^{(2)}c_4 \\
c^{(1)}c_1 & \lambda_1^2 & -c_1c_2 & -c_1c_3 & -c_1c_4 \\
c^{(1)}c_2 & -c_1c_2 & \lambda_2^2 & -c_2c_3 & -c_2c_4 \\
c^{(2)}c_3 & -c_1c_3 & -c_2c_3 & \lambda_3^2 & -c_3c_4 \\
c^{(2)}c_4 & -c_1c_4 & -c_2c_4 & -c_3c_4 & \lambda_4^2
\end{pmatrix}, \qquad (10)
$$

then

$$
T = \tfrac{1}{2}m\{\dot x^2 + \dot y^2 + \sum\sum f_{\rho\sigma} \cos(\theta_\rho - \theta_\sigma)\, \dot\theta_\rho\, \dot\theta_\sigma\}. \qquad (11)
$$

Hence, in the absence of constants, the dynamical equations take the form

$$
\begin{aligned}
m\ddot x &= m\,X\,, \\
m\ddot y &= m\,Y\,, \qquad (12) \\
m\sum_\sigma f_{\rho\sigma}[&\cos(\theta_\rho - \theta_\sigma)\ddot\theta_\sigma + \sin(\theta_\rho - \theta_\sigma)\,\dot\theta_\sigma] = m\,M_\rho\,,
\end{aligned}
$$

where the factors m are introduced on the right for convenience.

In case each extremity consists of n members, so that including the trunk there are $4n + 1$ members in all, the equations have still the same form, with ρ and σ running from 0 to $4n$. We designate the members as follows: starting with the trunk, to which we still assign the subscript 0, we enumerate the members of the left foreleg from 1 to n; the members of the right foreleg from $n + 1$ to $2n$; the members of the left hind leg from $2n + 1$ to $3n$; and the members of the right hind leg from $3n + 1$ to $4n$. The symmetric matrix $(f_{\rho\sigma})$ has then the form

$$\begin{array}{cccccccc}
\lambda_0^2 & c^{(1)}c_1 & \cdots & c^{(1)}c_{n+1} & \cdots & c^{(2)}c_{2n+1} & \cdots & c^{(2)}c_{3n+1} \quad \cdots c^{(2)}c_{4n} \\
\cdot & & & & & & & \\
\cdot & \lambda_1^2 & \cdots & -c_1c_{n+1} & \cdots & c_1c_{2n+1} & \cdots & -c_1c_{3n+1} \quad \cdots c_1c_{4n} \\
\cdot & \cdot & & & & & & \\
\cdot & \cdot & \cdots\cdots & \lambda^2_{n+1} & \cdots & -c_{n+1}c_{2n+1} & \cdots & -c_{n+1}c_{3n+1} \quad \cdots c_{n+1}c_{4n} \\
\cdot & \cdot & & \cdot & & \cdot & \cdots & \cdot \quad \cdot \\
\cdot & \cdot & & \cdot & & \cdot & \cdots & \cdot \quad \cdot \\
\cdot & \cdot & \cdots\cdots & \cdot & & \cdot & \cdots & \cdot \quad \cdot
\end{array}$$

We may suppose that in walking there is always at least one forefoot on the ground and always at least one hind foot on the ground, and that as soon as one of either pair is placed on the ground, the other is raised. Then there are always four equations of restraint, each relating a coordinate of S with the corresponding coordinate of a foot which is then stationary.

The movements M contain both the muscular forces and the frictional forces (including viscosity and wind-resistance). Those parts which depend upon the muscular forces alone must sum to zero. They depend upon the anatomical structure and upon the degree of innervation, as well as upon the velocity. In a steady state of movement we may suppose that this innervation varies with phase throughout each cycle, and since the velocities of rotation of the various members also vary with the phase, it is possible, formally at least, to express the movements as functions of the angles $\theta\rho$. However, these functions will be different for different speeds of locomotion by the same animal.

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BULLETIN OF
MATHEMATICAL BIOPHYSICS
VOLUME 7, 1945

A THEORY OF PHOTOSENSITIVITY OF SOME LOWER ANIMALS

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The two-factor nerve excitation theory is applied to the photoreactions of some lower animals along with the assumption that the threshold itself varies under the action of light, thus behaving formally like a third factor. The dependence of the reaction time upon the intensity of the stimulus is derived and is shown to follow the Bunsen-Roscoe law. The dependence of reaction time upon the time of exposure to light of a fixed intensity is derived and analyzed. The effect of dark adaptation upon the reaction time is analyzed quantitatively. Light adaptation and the effects of termination of exposure after light adaptation are discussed from the standpoint of this theory and the theory is found to be in agreement with observations.

Some lower animals react following an exposure to white light by suddenly contracting. The animal remains in a contracted state for a while and eventually shows adaptation by relaxing. In considering its reaction to light, two cases arise. The first case is that in which the exposure is continued until the reaction occurs and the second case is that in which the exposure is terminated before a reaction occurs.

In a series of papers, Selig Hecht (1918a, b, c, d; 1926; 1927) provides experimental data on the variation of the reaction time with the intensity of the stimulatory light in the first case, as well as the variation of the reaction time with the exposure time for a given light intensity in the second case, for *Ciona intestinalis*. Hecht also gives data showing the dependence of the reaction time upon the amount of time the animal has been in the dark following an initial long exposure to light. In this experiment the subsequent reactions were induced by a light of fixed intensity and the exposures were maintained until reactions occurred.

Our purpose in this paper is to present a theory which will account for the observed phenomena. This we shall do by assuming the following picture.

Suppose that when light of intensity I meter-candles reaches the sense cell on the periphery of the animal, the neurons leading from

this cell to various muscles will be affected by this stimulus and may eventually become excited. We shall further assume that following the excitation of these neurons, muscular contraction will occur after a time c_0 seconds. The time c_0 represents the interval between the arrival of impulses at the muscle and the instant the muscle begins to contract and is assumed to be constant.

Considering that the intensity I of the light plays the role of the intensity of a stimulus acting on a neuron of mixed type (Rashevsky, 1940, chapter vii), we may write

$$\frac{d\varepsilon}{dt} = KI - k\varepsilon; \tag{1}$$

$$\frac{dj}{dt} = MI - mj. \tag{2}$$

The factors ε and j are produced in a neuron of threshold h and we assume that excitation occurs when

$$\varepsilon - j \geqq h. \tag{3}$$

We shall make an additional assumption that the threshold h is affected by the light, and varies according to

$$\frac{dh}{dt} = NI - n(h - h_0), \tag{4}$$

where $h_0 > 0$.

The quantities K, k, M, m, N, and n are constants and it is assumed that the following inequalities between them hold:

$$K > M > > N > 0, \tag{5}$$

$$m > k > > n > 0, \tag{6}$$

$$0 < \frac{K}{k} - \frac{M}{m} < \frac{N}{n}, \tag{7}$$

$$Mm > Kk. \tag{8}$$

Furthermore, we shall suppose that N and n are so small that variations in h are appreciable only for very large values of the time. Thus no significant error will be introduced when h is regarded as a constant over short time intervals.

Consider what happens when at some time, when ε and j are equal to zero and $h = h_0$, the animal is exposed to light of intensity I meter-candles until a reaction occurs. Integrating equations (1) and (2), we obtain

$$\varepsilon = \frac{K}{k} I(1 - e^{-kt}), \tag{9}$$

$$j = \frac{M}{m} I(1 - e^{-mt}). \tag{10}$$

Since $K > M$, ε will increase more rapidly. We shall define t^* to be the minimal value of t, if it exists, for which

$$\varepsilon(t^*) - j(t^*) = h_0, \tag{11}$$

and we shall refer to t^* as the sensitization period. In case t^* is small, we may ignore all but the linear and constant terms in the expansion of e^{-kt^*} and e^{-mt^*}, and using equations (9) and (10), we may write equation (11) in the form

$$(K - M) I t^* = h_0. \tag{12}$$

Solving equation (12) for I, we have

$$I = \frac{h_0}{(K - M)} \cdot \frac{1}{t^*}. \tag{13}$$

In Figure 1 the comparison of equation (13) with S. Hecht's

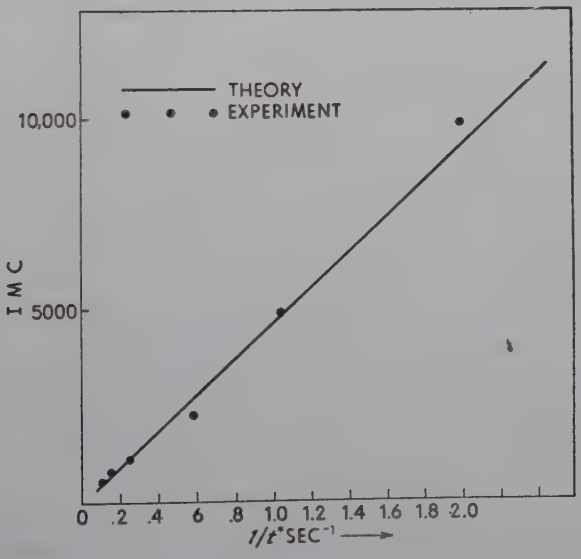

FIGURE 1

(1918a) data is made. Hecht's procedure was to measure the reaction time for a given stimulus intensity and then to compute the sen-

sitization time by subtracting 1.76 seconds from the reaction time. This amounts to assuming the value 1.76 seconds for c_0 in our theory. Hecht chose the value 1.76 seconds to make his calculations of t^* because it seemed to be the smallest value attainable for the reaction time. The line of Figure 1 is extrapolated into small values of I. Actually Hecht finds a minimal value of I for which a reaction will occur. For very weak intensities, t^* would be quite large and the approximations upon which equation (13) is based would not be expected to hold, hence precautions must be taken in applying equation (13).

Let us next consider the case in which the exposure is terminated before any reaction occurs. Let t' seconds be the length of exposure, then when exposure is stopped, we have

$$\varepsilon(t') - j(t') < h_0. \tag{14}$$

For small values of t', $\varepsilon(t')$ and $j(t')$ will be given by equations (9) and (10) as

$$\varepsilon(t') = KIt', \tag{15}$$

$$j(t') = MIt'. \tag{16}$$

Setting

$$\theta = t - t', \tag{17}$$

we have, after exposure ends,

$$\frac{d\varepsilon}{d\theta} = -k\varepsilon, \tag{18}$$

$$\frac{dj}{d\theta} = -mj, \qquad \theta \geqq 0, \tag{19}$$

with $\varepsilon = \varepsilon'$ and $j = j'$ when $\theta = 0$.

Integrating equations (18 and 19), we have

$$\varepsilon = KIt'e^{-k(t-t')}, \tag{20}$$

$$j = MIt'e^{-m(t-t')}. \tag{21}$$

Hence

$$\varepsilon - j = It'[Ke^{-k(t-t')} - Me^{-m(t-t')}]. \tag{22}$$

For $t \geqq t'$, ε will decrease less rapidly than j initially, since $Kk < Mm$, and $\varepsilon - j$ may thus continue to increase until $\varepsilon - j = h_0$. As before, letting t^* be the minimal time for which $\varepsilon - j$ equals h_0, we have

$$It'[Ke^{-k(t^*-t')} - Me^{-m(t^*-t')}] = h_0. \tag{23}$$

Considering again the case that $t^* - t'$ is small enough, expanding the exponential, and preserving only linear terms, we find from equation (23)

$$It'[K - M + (Mm - Kk)(t^* - t')] = h_0 . \tag{24}$$

Let us call the interval between the end of exposure and the reaction the latent period, and denote it by L. If T sec is the reaction time, we have

$$T = t^* + c_0 , \tag{25}$$

and also by definition

$$L = T - t' = t^* - t' + c_0 , \tag{26}$$

hence

$$t^* - t' = L - c_0 . \tag{27}$$

Introduction of expression (27) into equation (24) yields, after solving for L,

$$L = \frac{h_0}{I(Mm - Kk)} \cdot \frac{1}{t'} + c_0 + \frac{M - K}{Mm - Kk} . \tag{28}$$

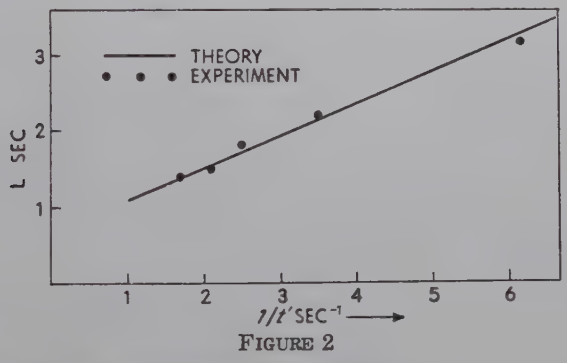

FIGURE 2

In Figure 2 we compare equation (28) with data obtained from Hecht (1926). The approximations upon which equation (28) is based restrict both L and t' to sufficiently small values. Except for very small values of I, a maximum value is imposed on t' by inequality (14). Likewise, a minimum value of t' always exists, for if

$$\varepsilon(t') < h_0 , \tag{29}$$

certainly no possibility remains that $\varepsilon(t) - j(t) = h_0$ for some $t > t'$.

Returning to equations (9) and (10), we note that as exposure to the light I is maintained indefinitely, the quantities ε and j approach the asymptotic values ε_a and j_a given by

$$\varepsilon_a = \frac{K}{k} I, \tag{30}$$

$$j_a = \frac{M}{m} I. \tag{31}$$

The quantity h will change according to the integral of equation (4) and will be given by

$$h = \frac{N}{n} I(1 - e^{-nt}) + h_0, \tag{32}$$

assuming that $h = h_0$ when $t = 0$.

As the exposure time increases, h approaches asymptotically the value h_a which is given by

$$h_a = \frac{N}{n} I + h_0. \tag{33}$$

In view of inequality (7), we may write

$$\varepsilon_a - j_a < h_a, \tag{34}$$

and conclude that adaptation will always occur.

Suppose that exposure to light of intensity I m.c. has been in effect for a very long time until ε, j, and h are very close to the values ε_a, j_a, and h_a given by equations (30), (31), and (33). Let the exposure be abruptly ended, and denote by θ' the time from the moment the exposure ends. The values of ε and j will be given as the integrals of equations (18) and (19) where the initial conditions are $\varepsilon = \varepsilon_a$ and $j = j_a$ for $\theta' = 0$. Hence we have

$$\varepsilon = \varepsilon_a e^{-k\theta'}, \tag{35}$$

$$j = j_a e^{-m\theta'}. \tag{36}$$

These two quantities drop to zero in a short period, so that we may regard h as constant and equal to h_a. From equations (35), (36), (30), and (31), we obtain

$$\varepsilon - j = \frac{K}{k} I e^{-k\theta'} - \frac{M}{m} I e^{-m\theta'}. \tag{37}$$

For $\theta' = 0$, $\varepsilon - j$ will be less than h_a because of inequality (34), so that if $\varepsilon - j$ is to exceed h_a it must increase as θ' increases. Since $\varepsilon - j$ will ultimately vanish, we know it will decrease again. Differentiating expression (37) and setting the derivative to zero, we obtain an equation for θ'_c, the value of θ' for which $\varepsilon - j$ has a maximum,

$$MIe^{-m\theta_c'} - KIe^{-k\theta_c'} = 0 . \tag{38}$$

Solving equation (38) for a finite value of θ_c' gives

$$(k - m)\theta_c' = \log \frac{K}{M}. \tag{39}$$

Since, by inequality (5), $K > M$, we have $\log(K/M) > 0$. But by inequality (6), $k < m$, hence $k - m < 0$. Therefore, $\theta_c' < 0$ and since θ' is non-negative, we may conclude that at no finite time after exposure will $d(\varepsilon - j)/d\theta'$ be equal to zero. Hence $\varepsilon - j$ is monotonically decreasing. From this and from inequality (34) we conclude that no reaction will spontaneously occur following termination of any exposure of long duration. However, in the period following exposure of long duration, reactions may be evoked by re-exposure for brief periods. As before, let $\varepsilon = \varepsilon_a$, $j = j_a$, and $h = h_a$ when exposure is ended. The quantities ε and j will rapidly approach zero and h will begin a slow descent towards h_0. At a time τ after exposuure has ended, h will be given by integrating equation (4) with $I = 0$, and $h(0) = h_a$:

$$h(\tau) = \frac{N}{n} Ie^{-n\tau} + h_0. \tag{40}$$

If τ is not too small, ε and j will be practically equal to zero. Let the animal be exposed to a light of intensity I' m.c. until a reaction occurs. Following the analysis leading to equation (13), we may write after replacing h_0 by $h(\tau)$,

$$t^* = \frac{NIe^{-n\tau}}{nI'(K - M)} + \frac{h_0}{I'(K - M)}. \tag{41}$$

Making use of expression (25), we obtain

$$T = \frac{NIe^{-n\tau}}{nI'(K - m)} + \frac{h_0}{I'(K - M)} + c_0. \tag{42}$$

If the time of exposure to I' is brief, the effect of I' on h will be negligible and we may assume that h obeys equation (40). Thus we may repeatedly expose the animal to light of intensity I' at widely separated value of τ and still make use of equation (42). Calling

$$\frac{NI}{nI'(K - M)} = A_0, \tag{43}$$

and

$$\frac{h_0}{I'(K - M)} + c_0 = b_0, \tag{44}$$

we may write

$$\log (T - b_0) = \log A_0 - n\tau . \qquad (45)$$

Hecht (1927) gives data on the variation of T with τ. By selecting an appropriate value of b_0 and graphing the experimental values of log $(T - b_0)$ against τ, a straight line is obtained as in Figure 3.

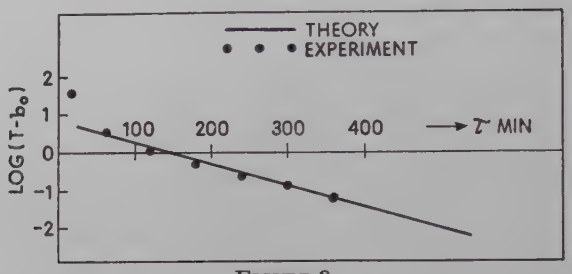

FIGURE 3

Thus by choosing suitable values for A_0, n, and b_0, equation (45) can be made to fit the experimental line.

Notice that in Figure 3 there is a considerable discrepancy between theory and experiment for $\tau = 15$ sec. The explanation of this discrepancy lies in the fact that for this relatively small value of τ, h has not changed much and that h_a may have been very large. Thus in order for $\varepsilon - j$ to exceed this large value of h, it would be necessary to maintain exposure until the non-linear variation of ε and j with time was reached. In such a case, the value of t^* given by the linear approximations to ε and j (the theoretical one) would fall short of the non-approximate value of t^*, so that the theoretical value of T would be too small. This is actually the case as can be seen by inspecting Figure 3.

Although the data of Figures 1, 2, and 3 are obtained from different groups of animals, it is of interest to compare the values of the constants occurring in equations (13), (28), and (45) which are used for the comparison.

Evaluating $h_0/(K - M)$ from the data of Figure 1 gives $h_0/(K - M) = 4{,}600$. In obtaining Figure 1, c_0 was taken equal to 1.76. In obtaining Figure 3, b_0 was taken equal to 2.1. Now $b_0 = c_0 + h_0/I'(K - M)$ and in Figure 3 we have an $I' = 6{,}000$ m.c., hence using the values of c_0 and $h_0/(K - M)$ of Figure 1, we find b_0 would be equal to 2.5 which, after taking into consideration the fact that we have two distinct groups of animals, compares favorably with 2.1. In Figure 2, the average value of $h_0/I(Mm - Kk)$ is equal to .41. Here we have $I = 10{,}000$ m. c., thus $h_0/(Mm - Kk) = 4{,}100$. Making use of the value of $h_0/(K - M)$ from Figure 1, we obtain

$(M - K)/(Mm - Kk) = -.886$. From Figure 2 we obtain an average of $c_0 + (M - K)/(Mm - Kk)$ equal to .68. Using $c_0 = 1.76$ from Figure 1, we then have $h_0/(Mm - Kk) = -1.03$, which compares favorably with $-.886$. These values are roughly computed and are used chiefly to compare orders of magnitude.

The data presented in Figures 1, 2, and 3 are for the ascidian *Ciona intestinalis*. Figures 2 and 3 represent typical results. S. Hecht (1918, 1927) experimented extensively with the clam, *Mya arenaria*, however, his results with this animal are not included here. A good agreement between this theory and the results Hecht gives for *Mya* is found for equations (13) and (45). In considering equation (28) applied to *Mya*, we find in graphing experimental values of L against $1/t'$ that the curve is increasing but has a negative second derivative and tends to become linear. However, as t' approaches zero, no reaction will occur after t' has fallen below a minimum value, and hence L must become infinite for a finite $1/t'$. Therefore the L vs. $1/t'$ curve must have an inflection point. It is in the region of the inflection point that our linear approximation holds. Possibly the range of values of $1/t'$ used in the experiments with *Mya* happens to fall below the linear range.

This work was aided in part by a grant from the Dr. Wallace C. and Clara A. Abbott Memorial Fund of the University of Chicago.

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BULLETIN OF
MATHEMATICAL BIOPHYSICS
VOLUME 7, 1945

OUTLINE OF A MATHEMATICAL APPROACH TO THE CANCER PROBLEM

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The fact that the growth of every organism, as it develops through cell multiplication from the ovum, eventually ceases, makes plausible the hypothesis that each cell of an organism exerts some kind of inhibitory influence upon the growth and multiplication of every other cell through the medium of some factor j. Each cell, however, is considered to possess an amount of a "growth factor" g, the activity of which is inhibited by j. In the course of development, most cells differentiate. A number of them remains relatively undifferentiated, and those are used for repairs of natural tear and wear as well as for healing of wounds. With age either the number of those cells or their "potency" decreases, which accounts for a general decrease in the speed of wound healing. Due to statistical fluctuations, the amount of the g is not uniformly distributed amongst the cells. Some of them have accidentally a greater amount than others. As the number or potency of the undifferentiated cells decreases with age, so does their inhibitory influence upon other cells. Therefore, those cells which do have an accidental excess of g–factor will begin to grow and multiply, producing neoplasms. Putting the above assumptions into mathematical form, it is possible to derive a relation which gives the *probability* of cancer incidence as a function of age. The theoretical relation is compared to the rather inadequate empirical data and found in agreement with them. A relation for the speed of wound healing as a function of age is also derived, and also found in general agreement with the rather scant data. Several other conclusions are discussed and possibilities of their practical applications pointed out.

The tremendous amount of cancer research has given us a great deal of information about the cytological, physiological, and biochemical peculiarities of the cancer cell. The studies of the peculiar characteristics of the carbohydrate metabolism of cancer cells seem particularly noteworthy. Yet, in spite of all this, no definite regularities have been found in regard to causal relationships of cancer to other biological manifestations of the organism. It almost looks as if *the* characteristic property of the occurrence of cancer is its statistical character. Rates of incidence of cancer at different ages are approximately known, but no possibility of predicting any individual case has yet been found. The pathologist, the physiologist, and the biochemist are interested in the details of the individual case. Questions of statistics of incidence of those cases do not interest them.

The statistician, on the other hand, is usually interested in collecting his statistical data, compiling figures and charts, and his work has apparently no relation to the physiological and biochemical studies. Yet behind every statistics there must be some physicochemical or biophysical cause which is responsible for a particular statistical distribution. Contrary to the belief of some non-mathematical biologists, discovery of statistical relationships does in no way constitute a theory, mathematical or otherwise. But there should be a rational biophysical theory to interpret and explain the various statistical relationships which are found empirically.

Perhaps one of the most conspicuous results of cancer statistics is the indication that in general the incidence of cancer is an increasing function of age. Even agreeing with a large number of skeptical clinicians that the cancer statistics are still extremely inaccurate, we feel that the data collected gives us, nevertheless, at least a rough idea of the distribution function of cancer incidence with age. A mathematical-biophysical theory which would represent this function correctly within the limits of error is worth considering.

It is generally agreed that the transformation of a normal cell into a cancer cell represents a return to a less differentiated quasi-embryonic condition. O. Warburg (1926) points out certain biochemical analogies between tumor cells and embryonic cells. It is also agreed that a cancer cell is characterized by its *going out of control* (Ewing, 1940) of the organism. The idea of some inhibitory effect which has suddenly been removed thus suggests itself. On the other hand, since the growth of an organism does not proceed indefinitely, but slows down and eventually comes to a standstill, the idea of a mutual inhibition of growth and multiplication by all growing and multiplying cells of the organism suggests itself. Suppose that the rate of growth and of multiplication of each cell is determined by some factor g, the exact physicochemical nature of which is for the present immaterial. Suppose, furthermore, that each cell of an organism exerts an inhibitory effect due to a factor j upon every other cell through the medium of some chemical substance. If we have n cells in an organism, we may consider that the rate of multiplication of each cell is proportional to $ag - b(n-1)j$, where a and b are two coefficients of proportionality, since $(n-1)j$ is the inhibitory effect upon a cell of the other $n-1$ cells. Hence

$$\frac{dn}{dt} = n[ag - bj(n-1)] = n[(ag + bj) - bjn]. \qquad (1)$$

The organism will cease to grow when

$$n = n_a = \frac{ag + bj}{bj}, \tag{2}$$

for then $dn/dt = 0$.

With C as an integration constant, the growth curve is given by

$$n = \frac{ag + bj}{C\, e^{-(ag+bj)t} + bj}. \tag{3}$$

Actually, the growth curves are represented by more complicated equations. Such may be readily obtained by considering the more general case, which corresponds better to reality, namely, that in each organism there are different types of cells, each having a different value of g and j, as well as different coefficients a and b. Moreover, after a certain stage, the growth of some parts of the organism proceeds principally through actual increase of cell volume, rather than through cell multiplication, and a complete theory of growth curves must take this into account. For our purposes we shall limit ourselves to the simple equation (1), remembering its limitations. The comparison of the theoretical results with observed data will be made more for purposes of illustrating the usefulness of the approach, rather than to claim any correct representation of the data. Those results should be later generalized in the manner indicated above.

Growth of the organism proceeds usually parallel with the differentiation of different cells. But even in an adult organism there remains a number n_u of relatively undifferentiated cells. Those are gradually used for repair of natural tear and wear as well as for the healing of wounds. Thus in general we would expect the number n_u of those cells to decrease with age, this decrease beginning approximately at the time when growth through multiplication ceases, and only growth through actual increase of the volume of the cells continues. Since in man some parts of the body, for instance bones, continue to grow by multiplication up to the age of 16-18 years, while others, such as muscles, grow after birth mostly through actual increase, the beginning of the above mentioned decrease is not sharply defined in this approximate theory, and may be put approximately at the age of 8-9 years. The simplest assumption about this decrease would be that it is linear with respect to time. We might then tentatively interpret the time at which n_u becomes zero, and after which no repair of the organism is possible, as the natural age limit. It seems, however, more plausible to assume an exponential decay, thus

$$n_u = n_{0u}\, e^{-ct}. \tag{4}$$

If c is sufficiently small then for not too large values of t we may ex-

pand the exponential function and preserve only the linear terms. This gives, as an approximation,

$$n_u = n_{ou}(1 - ct). \tag{5}$$

With the more general expression (4) the natural age limit, in this interpretation, is not sharply defined. Theoretically it is infinite, but as n_u becomes very small, the probability of surviving even a slight injury or wear becomes smaller. Thus the reciprocal of c may be considered as a measure of natural longevity.

In order to obtain the formal mathematical results which follow, it is not necessary to assume that the number n_u of undifferentiated cells decreases with time according to equations (4) or (5). It is possible that that number even remains constant, but that the *proliferating potency* of those cells decreases in the above mentioned way. For the subsequent deductions, the *actual* physiological mechanism is to some extent irrelevant. Therefore, *for simplicity,* we shall continue to speak of the *number* of undifferentiated cells, but it actually may be a different quantity, of a purely biochemical nature.

The decrease of n_u results in a decrease of n, the total number of cells in the organism. This results in a decrease of the inhibiting effect on other cells. Although it is not necessary to do so, yet we shall assume here that the inhibitory effect is produced principally, if not exclusively, by the relatively undifferentiated cells. Under those conditions, as the number n_u decreases with age, the number of other cells would increase according to equation (1). We must, therefore, conclude that with the process of differentiation the amount of the g-factor decreases so that in an adult organism there is a sufficient excess of the j-factor to prevent any cells from multiplying as n_u decreases.

If all cells would have the same amount of g-factor and if all other constants were the same, then as long as n_u (or the equivalent potency) remains above a certain threshold level, none of the cells will multiply, except when they are in some way removed from the influence of the j-factor. Such a situation may occur perhaps in the case of a wound.

There is some evidence for the existence of "wound hormones" which stimulate the proliferation of cells. In a complicated phenomenon like wound-healing, the following may also be a factor. The formation of a blood clot may reduce the circulation of the j-factor in the immediate neighborhood of the undifferentiated cells adjacent to the wound. Those cells receive now the j-factor only from a relatively smaller group of differentiated cells, and the inhibition of their multiplication may be sufficiently reduced to permit that multiplication.

Thus the cicatrisation of a wound begins and goes on until the normal circulation, and thus a normal supply of the j-factor, to all cells is restored. The differentiated cells, removed by the formation of the wound, are thus restored at the expense of the proliferating undifferentiated cells, whose number n_u decreases. It is noteworthy that keeping a wound washed so as to prevent the formation of the clot interferes with its healing. This is usually ascribed to the "washing away" of the wound hormones. But it is readily seen that it may be due, *at least partly,* to an effect like the one discussed above.

It may even be that the growth hormones act by inhibiting the formation or the activity of the j-factor.

On the basis of this picture we would expect that the rate w of wound healing would be roughly proportional to n_u, that is, it will decrease with age according to

$$w = w_0 e^{-ct}, \tag{6}$$

or for not too advanced ages according to

$$w = w_0(1 - ct). \tag{7}$$

Data on that subject are rather meager. Figure 1, taken from the work of P. Lecomte du Noüy (1937, p. 88) shows that relation (7) seems to be rather well-satisfied between the ages of 20 and 40.

If all the cells had the same amount of g-factor, then they either

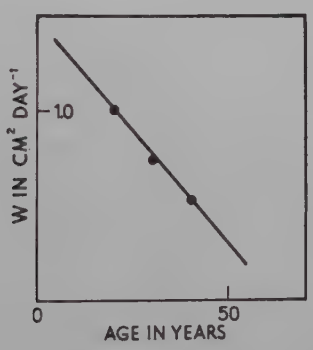

FIGURE 1

all would have their growth inhibited, or they all would be growing. If, however, different cells of the same kind have different amounts of g, then those with a sufficiently large amount will be still able to grow, though the ones with less g will not grow. The situation is *formally* identical with the interaction of excitation and inhibition in a set of unequally excited neurons (Rashevsky, 1938, chap. xxii).

Whatever the probably rather complex nature of the g-factor may be, its distribution amongst the different cells is likely to be determined in the early embryonic stages. Let $\bar{g}$ be the average amount of g for each cell. If all cells had the amount $\bar{g}$, their growth would be inhibited when the adult stage is reached. But due to physicochemical fluctuations, some cells will have an excess g_1 or a deficiency $-g_1$ over $\bar{g}$. Assuming random fluctuations, which lead to a normal distribution of $\bar{g}$, we would have for the number N of cells, which have a g_1 between g_1 and dg_1, the expression

$$N(g_1)\,dg_1 = Ae^{-\sigma g_1^2}\,dg_1\,. \tag{8}$$

The cells with a negative g_1 remain inhibited, but those with a positive g_1 may grow even in an adult organism if g_1 is sufficiently large. In order for a cell with a given g_1 to grow it is necessary that $\bar{g} + g_1 > j$. But if j is proportional to n_u, then it follows from expression (4) or (5) that

$$j = j_0 e^{-ct} \quad \text{or} \quad j = j_0(1 - ct). \tag{9}$$

Expression (8) gives the probability of a cell or group of cells having a given g_1. If the value $\bar{g} + g_1$ becomes equal or exceeds the value of j, given by equations (9), that cell or group of cells will grow. Hence the probability $W(t)$ that a given cell or group of cells will begin to grow on or after a given time t is obtained by substituting for g_1 into equation (8) the quantity $j - \bar{g}$, where j is given one of the expressions (9). This gives

$$W(t) = Ae^{-\sigma(j_0 e^{-ct} - \bar{g})^2} \quad \text{or} \quad W(t) = Ae^{-\sigma[j_0(1-ct) - \bar{g}]^2}. \tag{10}$$

It is readily seen that $W(t)$ increases with t.

Somewhat simpler relations are obtained if instead of a normal distribution we assume a simple exponential

$$N(g_1) = A_1 e^{-\sigma|g_1|}\,dg_1\,. \tag{11}$$

H. D. Landahl (1938) has pointed out that except for very small values of g_1, the expression (11) can be used as a very good approximation of equation (8). Putting

$$A_1\, e^{-\sigma(j_0 - \bar{g})} = A_2; \qquad \sigma\, j_0 c = \alpha\,, \tag{12}$$

and omitting the absolute value sign, since only for positive values of g_1 there can be $\bar{g} + g_1 > j$, we now have instead of equations (10) the following expression:

$$W(t) = A_1\, e^{-\sigma(j_0 e^{-ct} - \bar{g})} \quad \text{or} \quad W(t) = A_2\, e^{\alpha t}\, dt. \tag{13}$$

Expressions (13) give us the probability of a cell or group of cells to begin to grow and to go out of the inhibitory control of the organism, as a function of the age t.

Data by F. L. Hoffman (1915) indicate that within a fairly large range of t the second simpler equation (13) describes rather well the incidence of cancer as a function of age. If the second equation (13) were to hold exactly, then we should obtain a straight line with positive slope by plotting W against t on a semi-logarithmic paper. Actually, such graphs begin to deviate from a straight line for advanced ages. Such a deviation would be expected from the first equation (13). A compromise equation between the two takes care of the situation. If we expand e^{-ct} and break off after the quadratic terms, we find

$$e^{-ct} = 1 - ct + \tfrac{1}{2} c^2 t^2 . \tag{14}$$

Introducing this into the first equation (13), we obtain

$$W(t) = A_3 \, e^{\alpha t - \frac{1}{2}\alpha c t^2} \, dt , \quad A_3 = A_1 \, e^{-\sigma(j_0 - \bar{g})} . \tag{15}$$

Equation (15) gives

$$\log W(t) = \log A_3 + \alpha \, t - \tfrac{1}{2} \alpha \, c t^2 . \tag{16}$$

Figure 2 illustrates how equation (16) represents actual observations. The ordinates represent cancer incidence for males for all organs, per

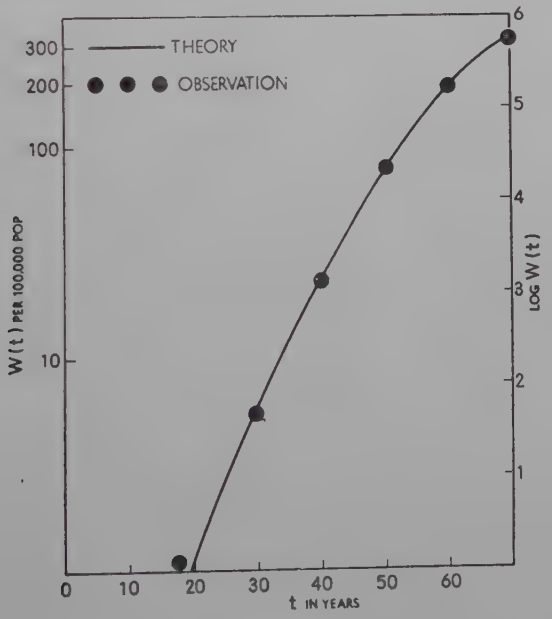

FIGURE 2

100,000 population (Hoffman, 1915, p. 231), plotted on logarithmic scale. The theoretical curve has the following parameters: $\log A_3 = -4.2$; $\alpha = 0.236$ year^{-1}; $c = 0.011$ year^{-1}; this gives for the normal longevity $1/c = 88$ years, which is of the correct order of magnitude. It is important that we thus can correctly compute the human normal longevity from data on cancer incidence. Data for females and total population give similar results.

Another result of the cancer statistics is that the incidence of cancer varies greatly for different organs and locations. The cancer of liver and stomach has the highest incidence. Next comes the intestinal tract, then the buccal cavity. Cancer of the extremities and of the brain is particularly rare (Hoffman, 1915). On the basis of the proposed theory, this must be interpreted as indicating that the g-factor is formed during the early embryonic stages in that part of the embryo which gives eventually rise to the stomach and liver. From there the g-factor is spread either by some process of diffusion, or is carried by proliferating cells into other parts of the embryo. Its excess therefore will be greatest in the stomach-liver region, and the probability of a given g_1 will now be a function not of g_1 only, but also of the distance r within the embryo from the stomach-liver region. We thus shall now have instead of equation (15) an expression of the form

$$W(t, r) = A_3 f(r) e^{at - \frac{1}{2}act^2}. \tag{17}$$

In the further development of the theory it will be indicated to derive an expression for $f(r)$ from some theoretical assumptions.

As we said above, the j-factor is conceived to be some chemical substance (or substances) produced principally by the less differentiated cells and carried by the blood stream. Let us consider the case when the production of the j-factor is constant, going on at a rate Bn_u, B being a constant. Like most of such substances it is likely to undergo a decomposition in the blood stream. If j is measured per unit volume, and if V is the total volume of the blood stream, then, assuming a monomolecular reaction, we have, denoting by k a constant

$$V \frac{dj}{dt} = Bn_u - kVj. \tag{18}$$

Hence the stationary value $\bar{j}$ of j is equal to

$$\bar{j} = \frac{Bn_u}{Vk}, \tag{19}$$

and is proportional to n_u.

Things happen in this way, however, only when the j-factor is introduced into the blood stream at every point of the latter's surface. If a part of the blood stream traverses a region which does not contain any cells producing the j-factor, then the concentration of j will be less in that region. The actual distribution of the j-factor will depend on the details of the geometry of the blood stream and on the velocity of streaming. A very rough idea of what happens may be obtained by considering the following simple case.

Let the blood flow with a speed v cm sec^{-1} through a cylindrical blood vessel of radius R, whose axis we choose as the z-axis. Let at the input end of the vessel, where $z = 0$, the concentration of j be $\bar{j}$, but no j is poured into the blood vessel all along its length. The amount of j entering a cross-section at a point z is equal to $\pi R^2 v j(z)$, while the amount leaving through the cross-section at $z + dz$ is equal to $\pi R^2 v j(z + dz) = \pi R^2 v [j(z) + (dj/dz)\,dz]$. The total rate of change of the amount of j contained in the volume $\pi R^2 dz$, that is, the quantity $\pi R^2 dz\,(dj/dt)$ is equal to the difference between inflow and outflow less the amount $\pi R^2 kj dz$ destroyed by chemical reaction. Hence

$$\frac{dj}{dt} = -v\frac{dj}{dz} - kj,$$

or, for a stationary state,

$$v\frac{dj}{dz} = -kj. \tag{20}$$

Integrated this gives

$$j = \bar{j}e^{-\frac{k}{v}z}. \tag{21}$$

We see that only k and v determine the drop of j along the blood vessel. If the concentration j must drop below a fraction μ of $\bar{j}$ in order to make possible the growth of any cells along the blood vessel, then we must have

$$\mu = e^{-\frac{k}{v}z}$$

or

$$z = \frac{v}{k}\log\frac{1}{\mu}\ (>0). \tag{22}$$

Equation (22) may be considered as giving approximately the size of a region which must be deprived of the indifferentiated cells (or of their potency) in order that any other cell may start growing

without inhibition. We may consider that the effect of the carcinogenic substances is to destroy the production of j by the undifferentiated cells. In that case, we see that the size of the place to which the substance is applied should be roughly proportional to v/k. If this size is less than a certain value, there will always remain enough j-factor present to prevent any growth. We do not know if any experiments in regard to the effect of the size of the area, to which a carcinogenic substance is applied, upon the effectiveness of the application. The above considerations definitely suggest such experiments.

Sometimes the application of a carcinogenic substance at one place results in the formation of cancer at an adjacent place which is not directly affected by the substance. This may be readily understood on the basis of the above theory. A local destruction of the potency of the undifferentiated cells will somewhat reduce the j-factor also in its immediate neighborhood. If in that neighborhood there happens to be a cell or group of cells with a g_1 much larger than that present in the directly affected area, then growth will start in that neighboring area, rather than in the directly affected one.

Equation (22) would enable us to determine the constant k, if v, and z are known. While no special determinations of z have been made, it is plausible to take it of the order of magnitude of 1 cm. The fraction μ is likely to be of the order of $\frac{1}{2}$ to $\frac{1}{3}$. Taking for v the value 0.1 cm sec^{-1}, which is the average value for capillary circulation (Oppenheimer and Pincussen, 1925, p. 133), we find

$$k \backsim 0.1 \text{ sec}^{-1}.$$

Thus the j-factor, left to itself without being replenished, would be practically completely destroyed in a matter of a minute. If the value of z is smaller, the value of k becomes even higher.

The following may serve as an illustration as to how purely statistical data may be used for the evaluation of some biophysical constants, entering into the theory. There is evidence (Hoffman, 1915, 1937) that the incidence of cancer of the buccal cavity is increased by smoking. This can be interpreted as indicating that smoking, like any continuous irritation, increases locally the value of c in expressions (4), (5), or (9). The increase would be proportional to the amount x of tobacco consumed per unit time. Thus we may put

$$c = c_0 - c_1 x . \qquad (23)$$

If there were any data on the differences of cancer incidence for different amounts of tobacco consumption, the value of c_1 could be calculated in the following way.

For simplicity, let us confine ourselves to the approximate case corresponding to the second equation (13). The more general case is treated in a similar way. We have now for $W(t, z)$ instead of equation (17) the following expression for the incidence of cancer in absence of any irritant:

$$W(t, r) = A_3 f(r) e^{\alpha' t}. \tag{24}$$

We write α' instead of α because α' has now a "local" meaning, and is not the same as α. The distance r and the function $f(r)$ are evaluated for the buccal cavity. The total incidence of cancer of the buccal cavity during a given lifespan t^* is then given by

$$\overline{W}(r) = A_3 f(r) \int_0^{t^*} e^{\alpha' t}\, dt = \frac{A_3 f(r)}{\alpha} (e^{\alpha' t^*} - 1). \tag{25}$$

For a given rate x of continuous tobacco consumption we obtain the value of the total incidence $\overline{W}_x(r)$ by introducing into equation (24) the expression (12) for α', then substituting the value of c from equation (23), and again integrating from 0 to t^*. This gives

$$\begin{aligned} \overline{W}(r) &= A_3 f(r) \int_0^{t^*} e^{\sigma j_0 (c_0 + c_1 x) t}\, dt \\ &= \frac{A_3 f(r)}{\sigma j_0 (c_0 + c_1 x)} (e^{\sigma j_0 (c_0 + c_1 x) t^*} - 1). \end{aligned} \tag{26}$$

The value of t^* may have to be corrected for different longevity as a function of x, according to R. Pearl (1938).

Since $A_3 f(r)$, σj_0, and c_0 are constants, therefore equation (26) represents the dependence of the incidence of cancer of the buccal cavity on the average rate x of continued smoking. *If adequate data were available,* equation (26) could be compared with those and the constants, including c_1, could be determined.

This shows in principle how purely statistical data may acquire a biophysical importance when used in conjunction with a proper theory.

Similar considerations may be applied to the study of the differences in cancer incidence in various professions. The effects of different professions upon the constant c may thus in principle be determined, if the statistical data were adequate.

The constant c in equations (4) and (5) is, as remarked, related

to natural longevity. The latter is definitely known to be determined genetically. It is natural to assume that the constants σ and A (or A_1) are also determined genetically. This opens a way to a mathematical theory of the genetics of cancer, which thus becomes naturally connected to the genetics of longevity. This may throw some interesting theoretical light on the studies of Maud Slye (1937, 1941).

Because of the practical importance of the cancer problem, one may legitimately ask whether the outlined theory suggests, at least as a working hypothesis, any new approaches to the problem of prevention and cure of cancer. From our estimates of the value of k, it follows that even if the biochemists synthetise the j-factor, any injection of the latter into an organism in which its production is deficient would be useless. For the same reason it appears hopeless to isolate the j-factor. It may of course be possible to find another substance which has the same growth inhibitory properties, but is much more stable.

There is, however, one possibility which, to our knowledge, has not yet been considered. If the j-factor is the thing that limits the growth of an organism, then it is likely that it is present also in some unicellular organisms which grow to colonies of a limited size. It is of course possible that for each type of cell there is a specific j-factor. This may be investigated by studying possible growth inhibiting effects of one type of cells upon another. If such studies would show that the j-factor is non-specific or has a non-specific component, then a prevention or cure of cancer may be effected by injecting into the blood stream a sufficiently large amount of appropriate microorganisms producing the j-factor. They must be so chosen that they would not produce immediate antigenic reactions nor be phagocitized too rapidly. While the j-factor alone would be destroyed almost instantaneously, it may be possible to find a proper microorganism which would last in the blood stream for a sufficiently long time to make the necessary injections not too frequent. The theoretical study of the interaction between such a microorganism and phagocytes, somewhat similar to the one made by H. D. Landahl (1944) for malaria, may be pertinent to the problem.

This work has been aided in part by a grant from the Dr. Wallace C. and Clara A. Abbott Memorial Fund of the University of Chicago.

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BULLETIN OF
MATHEMATICAL BIOPHYSICS
VOLUME 7, 1945

NEURAL MECHANISMS FOR THE CONCEPTS OF DIFFERENCE AND SIMILARITY

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A neurobiophysical mechanism which reacts to *differences* in different modalities of a stimulus pattern is suggested. Another mechanism is suggested which reacts to *similarity*. The latter is measured by the number of neurons in common to the two stimulus patterns.

Consider a pair of stimulus patterns S_a and S_b, each containing as their components stimuli of different modalities which we shall designate by the subscript i. Thus we may write

$$\begin{aligned} S_a &= S_a(S_{a1}, S_{a2}, \cdots S_{ai}, \cdots), \\ S_b &= S_b(S_{b1}, S_{b2}, \cdots S_{bi}, \cdots). \end{aligned} \tag{1}$$

Two stimuli S_{ai} and S_{bi} of the same modality i in general involve two different afferent pathways. Thus we may have sensations of touch from different parts of the skin, or, in principle, visual sensations from different parts of the retina. Two stimuli of the same modality may, however, differ only in intensity. For this case a mechanism has been discussed by N. Rashevsky and developed in detail by A. S. Householder (Householder and Landahl, 1945) which provides that stimuli of different intensities excite different groups of neurons somewhere in the brain. Hence either already at the afferent level or at a higher level, we may consider two stimuli of the same modality as involving two distinct pathways.

It is even more likely that the two stimuli S_{ai} and S_{bi} will be separated *temporally*, affecting otherwise the same afferent end organ. In that case, we should consider a mechanism discussed previously (Landahl, 1940) which again results in a *spatial* separation of the two stimuli in the central nervous system.

Let us consider, therefore, a pair of stimuli S_{ai} and S_{bi} of the same modality, each affecting a separate pathway, as shown in Figure 1 in which as usual the full lines denote excitatory fibers and the broken lines, inhibitory fibers. If the constants of all fibers are the

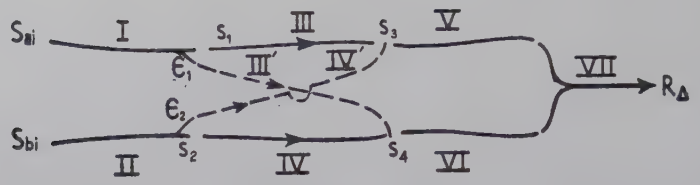

FIGURE 1

same, in particular if $A = B$ and $a = b$, then, as has been shown previously (Landahl, 1938, 1939), the net excitation at the synapses s_3 and s_4 is zero when $S_{ai} = S_{bi}$ or when $|S_{ai} - S_{bi}| = 0$. Let fibers *V* and *VI* synapse to a common path. Then if $\Delta_i = |S_{ai} - S_{bi}| = 0$, the fiber *VII* remains unexcited. If, however, Δ_i is sufficiently larger than zero, a reaction R_Δ is produced via fiber *VII*. We may say that the organism perceives the difference Δ_i between S_{ai} and S_{bi} if it produces the reaction R_Δ. In other words, R_Δ indicates the perception of the difference Δ_i. From the above scheme it follows that the larger Δ_i, the stronger will be R_Δ.

We may now introduce as before (Landahl, 1938; Rashevsky, 1940) the fluctuations of the quantities ε_1 and ε_2. Again because of the symmetry of the structure we do not restrict the generality of our results by considering the fluctuations of ε_1 only.

In order to produce the response R_Δ, either fiber *V* or fiber *VI* must be excited. This requires that (Landahl, 1938) $\varepsilon_1 - \varepsilon_2 > h$, or $\Delta_i > h_i$, where h is the threshold value determined by the different constants of all fibers, and h_i is another constant proportional to h. The natural fluctuations of excitation at the synapse s_2 result in temporary increases of ε_1 by an amount $(\varepsilon - j)'$. Let $p(\varepsilon - j)'d(\varepsilon - j)'$ be the probability of having the fluctuation lie between $(\varepsilon - j)'$ and $(\varepsilon - j)' + d(\varepsilon - j)'$.

If the standard deviation σ of the distribution function $p(\xi)$ is small as compared with h_i so that large fluctuations occur very rarely, then the probability of the reaction R_Δ to occur for very small values of Δ_i is very small. In order to produce the response R_Δ, or to recognize the difference Δ_i with a high degree of certainty, Δ_i must be sufficiently larger than 3σ and h_i must be smaller than σ. If $\Delta_i < h_i$, then in the absence of fluctuations there would be no response R_Δ; in other words, the difference between S_{ai} and S_{bi} is not perceived.

For each modality i we have a mechanism as described above. Let the fibers *VII* of all modalities converge to a final common path, which produces a reaction $R_{\Delta T}$. This latter reaction then may be con-

sidered as corresponding to the total difference between the stimuli S_a and S_b.

Let the afferent pathways which receive the stimuli S_{ai} and S_{bi} also be connected to a mechanism shown in Figure 2. Let each of the

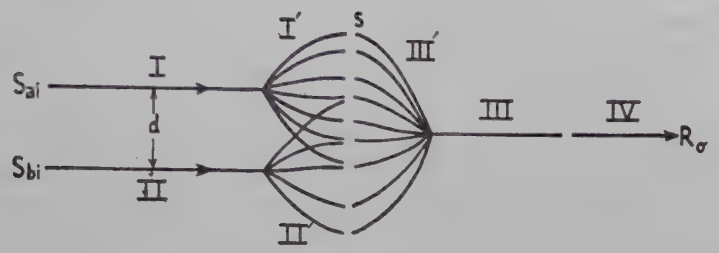

FIGURE 2

fibers *I* and *II* send off a large number of collaterals *I'* and *II'*, which all reach their saturation value E_S of excitation E for rather small values of S_{ai} and S_{bi}. Let those fibers *I'* and *II'* each synapse with a fiber *III'*, and all fibers *III'* converge into a common path *III*.

The asymptotic value $(\varepsilon - j)_a$ of $\varepsilon - j$ produced at the synapses s is proportional to E_S. For simplicity and without loss of generality, we shall choose our units so that $(\varepsilon - j)_a = E_S$. We shall use the same notation throughout this paper.

Let h_3 be the threshold of fibers *III'*, and let

$$E_S < h_3 < 2E_S . \tag{2}$$

Then only those fibers *III'* will be excited which synapse with both *I'* and *II'*. The number of such fibers will be smaller the greater the spatial distance d_i between *I* and *II*. The functional relation of that number with d will depend on the spatial distribution function of the fibers *I'* and *II'*. Hence the intensity of excitation E_{3i} of fiber *III* will in general be proportional to some quantity $\gamma(d_i)$ or

$$E_{3i} = a_i\, \gamma(d_i) = a_i\, \gamma_{0i}(1 - \beta_i\, d_i - \cdots), \tag{3}$$

where $\gamma(d_i)$ is a function which decreases with decreasing d_i and a_i, β_i and γ_{0i} are positive coefficients.

Let h_{4i} be the threshold of fiber *IV* and let

$$h_{4i} < a_i\, \gamma_{0i} = h_i' + h_{4i}, \tag{4}$$

where h_i' is a positive constant.

Then using only the linear terms of expansion (3) and denoting $E_{3i} - h_{4i}$ by σ_i, we find

$$\sigma_i = E_{Si} - h_{4i} = h_i' - a_i \beta_i \gamma_{0i} d_i . \tag{5}$$

The quantity σ_i is the greater, the closer S_{ai} and S_{bi} or the smaller d_i. Hence σ_i may be taken as a measure of similarity since $R_\sigma = 0$ for $\sigma_i \leqq 0$, therefore no similarity is perceived when d_i is sufficiently large.

Introducing

$$H = \sum_i h_i' , \tag{6}$$

we may define the *total* similarity by

$$\sigma_T = \sum_i \sigma_i = H - \sum_i a_i \beta_i \gamma_{0i} d_i . \tag{7}$$

Thus a pair of stimuli S_a and S_b sets into action two mechanisms: a difference mechanism represented in Figure 1, and a similarity mechanism represented in Figure 2.

If S_a is conditioned to a reaction R_a, and if σ_T is very large, then S_b will also produce the reaction R_a. For sufficiently small values of σ_T, S_b will not produce R_a. But if we consider statistical fluctuations of the values E_S or of the thresholds h, then there will always be a finite probability of S_b producing R_a, though that probability will decrease with decreasing σ_T.

To provide a mechanism which gives such a substitution of S_b for S_a, we must complicate somewhat the scheme shown in Figure 2. Let each synapse s excite, besides a fiber *III'*, an additional fiber having the same threshold as *III'* but leading to a conditioning center through which S_{ai} or S_{bi} may be conditioned to any reaction R_a. Then the more synapses S_{ai} and S_{bi} have in common, the more readily S_{bi} may replace S_{ai} to produce reaction R_a, and conversely.

Suppose now that the fiber *VII* of Figure 1 sends inhibitory fibers to the synapses s of Figure 2. Then if the difference reaction R_Δ is strong, the common connection between *I* and *II* on one hand and *IV* on the other will be inhibited. Since σ_i depends on the intensity of excitation of those common connections, therefore σ_i and σ_T will be weakened or completely inhibited. At the same time the substitution of S_b for S_a will be made impossible, or its probability greatly reduced. Hence if Δ_i is large but σ_i small, no substitution of S_b for S_a is possible. On the contrary, if σ_i is large and Δ_i is small, then S_a and S_b are readily substituted for each other; in other words, the organism behaves as if S_a and S_b were *identical*. Actually, no two stimuli can be completely identical and have $\Delta = \sum_i \Delta_i = 0$ because there are always at least spatial or temporal differences contributing to Δ. In

abstract thinking certain differences are sometimes intentionally disregarded. This may be accomplished by means of a center C which sends inhibitory fibers that inhibit the inhibitory connection between fibers *VII* of Figure 1 and the synapses s of Figure 2.

If the inhibition from C is too great, or if the path between *VII* and s is partially obstructed, then a substitution of S_b for S_a may take place even though Δ may be large and σ not too large. This will result in a "confusion" or "wrong identification".

The mechanism is based essentially on a competition between perception of similarity and that of difference. In inductive reasoning and synthetic science we usually do *look* for similarity rather than for differences. This *looking for similarities* may be interpreted as being the psychological equivalent of the activity of the center C, which must be assumed to be under voluntary control. We may also say that in this case we are conscious of the activity of the center C, which makes us aware of the fact that we are intentionally looking for similarities in two objects which are not perfectly identical. If C acts involuntarily and without our awareness of its activity, or if the activity of the difference mechanism is otherwise impeded, two different objects are perceived as identical, and confusion results.

In exact language and in logical thinking it is required by definition that even for a large value of σ_T two stimuli are considered as equivalent, $S_a \equiv S_b$, only if all the Δ_i's are less than or of the order of the corresponding h_i's with the exception of a group of i's, such as the spatial or temporal modalities, the differences in which are more or less arbitrarily considered as "unessential". The rules of the language determine which i's are to be excluded (by means of the center C).

In terms of the above discussed mechanism, we may say that if for a *non-excluded* i, Δ_i is sufficiently larger than h_i, it must inhibit completely the R_σ reaction. It seems to be necessary to assume that any Δ_i inhibits not only σ_i, but all the other σ_k's. Otherwise, a strong difference in one modality will still result in a possibility of a replacement reaction.

Since the mechanisms for perception of difference and of similarity are independent, there may be a region in which S_a and S_b are far enough apart so that all σ_i's and hence σ_T's are very small, and yet the difference $\Delta = \sum \Delta_i$ may be fairly small.

This work has been aided in part by a grant from the Dr. Wallace C. and Clara A. Abbott Memorial Fund of the University of Chicago.

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BULLETIN OF
MATHEMATICAL BIOPHYSICS
VOLUME 7, 1945

A HETERARCHY OF VALUES DETERMINED BY THE TOPOLOGY OF NERVOUS NETS

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Because of the dromic character of purposive activities, the closed circuits sustaining them and their interaction can be treated topologically. It is found that to the value anomaly, when A is preferred to B, B to C, but C to A, there corresponds a diadrome, or circularity in the net which is not the path of any drome and which cannot be mapped without a diallel on a surface sufficient to map the dromes. Thus the apparent inconsistency of preference is shown to indicate consistency of an order too high to permit construction of a scale of values, but submitting to finite topological analysis based on the finite number of nervous cells and their possible connections.

The term "reflex" originally meant a disturbance which, initiated by an extra-nervous organ, returned by a nervous path to that same organ. The law of Bell-Magendie, that impulses enter the nervous system by dorsal and emerge by ventral roots, specified the direction of conduction of these circular disturbances. Circular propagation in this direction was called dromic, in the opposite, antidromic. With the possible exception of phenomena comparable to that described by Porter, no response of any effector has ever indicated an antidromic reflex although conduction in the reverse direction has been demonstrated in both the dorsal and ventral roots.

The term "reflex" has latterly been used of any activity in which one pylon was extra-neural regardless of whether or not it was somatic. Lack of anatomic continuity about the external pylon let aftercomers ignore the essential circularity. All reflexes are dromes, activities of feed-back mechanisms, and consequently their function includes all purposive activity.

In addition to reflexes, there exist within the central nervous system reverberating circuits which for brevity are called endromes. Endromes are not in general so related to reflexes as to be uniquely syndromic or antidromic. Their temporal importance in determining the formal properties of nervous activity has been previously discussed (McCulloch and Pitts, 1943). Concerning endromes as well as reflexes, it is well to recall that a given feed-back circuit may be re-

generative for one temporal combination of excitations and degenerative for another.

Obviously any number of parallel circuits may be utilized by a single drome and these circuits may divide and unite without the disturbance ceasing to be dromic. Anatomically, the nervous components of their paths consist of neurons so related that the disturbance passes from neuron to neuron over a synapse from the axonal terminations of one neuron to the cell body of the next. With questionable propriety, the terms dromic and antidromic have been applied to passage across a synapse in this and the reverse direction respectively. The impropriety arises from the interrelation of two or more dromes. Conduction in each is dromic, in both, syndromic, but from one to the other, whether it facilitates or inhibits, it is properly neither syn- nor anti-, but heterodromic. Without heterodromic activity reflexes would occur independently of one another. It is therefore to these that one must look for sub-, super-, or co-ordination of reflexes; and, therefore, for behavior, including all relevant aspects of purposive activity.

For the following discussion, it is unnecessary to distinguish homeostatic from appetitive activity. One may even ignore the asymmetry of adversion and aversion, but it is essential to remember that the circuit, whether regenerative or degenerative, must be closed for its activity to be purposive. Thus, in its simplest form, any drome maps in a plane as in Figure 1.

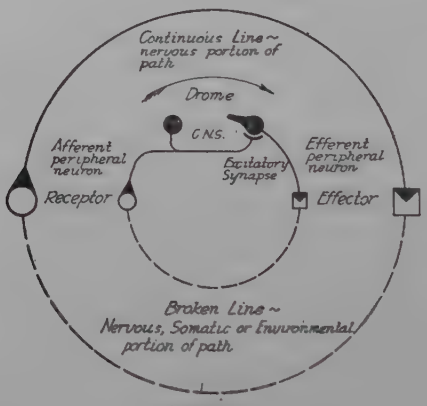

FIGURE 1

For a theory of valuation to be scientific, it must rest on observation and lead to prediction. Empirically, one must observe choice. Choice implies that two or more potential acts are incompatible. The observation requires some overt act with inhibition of incompatibles.

There must then be two complete circuits and an inhibitory, heterodromic influence from the one (for an overt act) to the other (for an incompatible act). The circuit maps as indicated in Figure 2.

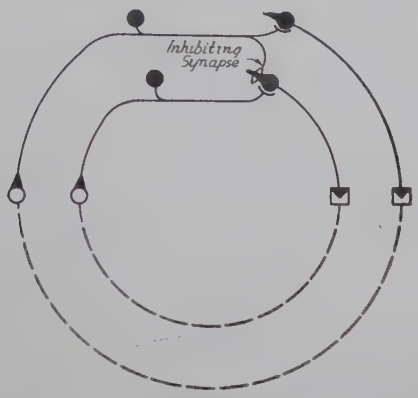

FIGURE 2

This scheme can be elaborated for any number of circuits arranged in order of dominance of dromes of each over all within it as in Figure 3.

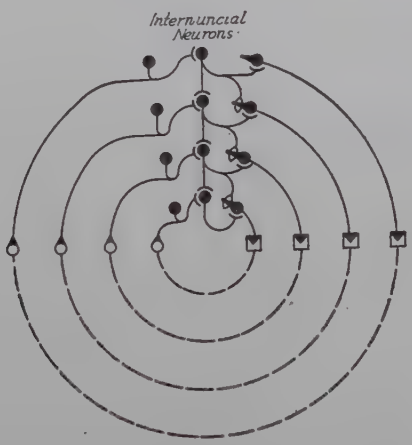

FIGURE 3

This figure in which heterodromic paths between parallel circuits require no diallels, or "crossovers", demonstrates that any hierarchy of values indicated by choice requires only a nervous net that maps on a plane. The term "hierarchy" in this context has two implications; each drome determines some aim, goal or end, and no two dromes determine exactly the same end. Because organisms live for these

ends, they are appreciated by them neither as means to other ends nor as conduct forced upon them, but rather as having that kind of power or importance which culminated in the notion of the sacred or holy—this is the religious implication of "hierarchy" as applied to values. The second implication, arising from the sacerdotal structure of the church, is that the many ends are ordered by the right of each to inhibit all inferiors. The number of ends, although large, is finite. The order is such that there is some end preferred to all others, and another such that all are preferred to it, and that of any three if a first is preferred to a second and a second to a third, then the first is preferred to the third. Logically, therefore, to assert a hierarchy of values is to assert that values are magnitudes of some one kind. Summarily, if values were magnitudes of any one kind, the irreducible nervous net would map (without diallels) on a plane.

Ever since theories of value deserted the inadequate, rational or proportional, Platonic approach, they have been notably inferior to intuition in inferring the outcome of an untried choice. Examination of the theories uncovers that values have been subsumed to be magnitudes of some one kind. Experimental aesthetics, economics, and conditioned reflexology have produced instances in which, under constant condition, preference was circular. One such instance would have been sufficient basis for categorical denial of the subsumption that values were magnitudes of any one kind. Thus, for values there can be no common scale.

Consider the case of three choices, A or B, B or C, and A or C in which A is preferred to B, B to C, and C to A. The irreducible nervous net is shown in Figure 4.

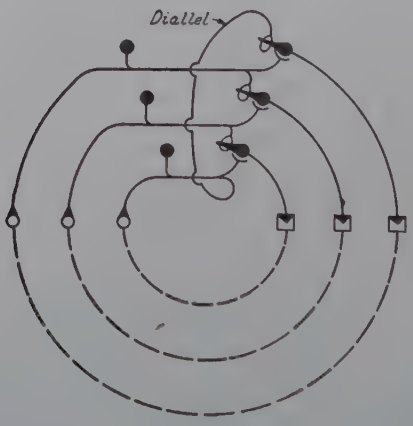

FIGURE 4

It requires one diallel in the plane. Its three heterodromic branches link the dromes so as to form a circle in the net which is distinguished from an endrome in that it is not the circuit of any drome but transverse to all dromes, i.e., diadromic. The simplest surface on which this net maps topologically (without a diallel) is a tore. Circularities in preference instead of indicating inconsistencies, actually demonstrate consistency of a higher order than had been dreamed of in our philosophy. An organism possessed of this nervous system— six neurons— is sufficiently endowed to be unpredictable from any theory founded on a scale of values. It has a heterarchy of values, and is thus internectively too rich to submit to a *summum bonum*.

Topological analysis of the intricacies of values implied by interlocking circularities of preference or of the equivalence of diallels in circuits to the surface on which the nets map without diallels are alike beyond the scope of the present article. Yet, it seems pertinent to note that, however complicated, the ultimate solution is finite even in man. The number of neurons in the brain is some 10^{10} and the number of irreducible diallels is presumably smaller. Let us suppose the worst of possible conditions. In the case of a circular preference, for 3 items, 1 diallel mediates 1 diadrome; for 4 items, 3 diallels mediate 4 diadromes; for 5 items, 6 diallels mediate 7 diadromes; for 6 items, 10 diallels mediate 15 diadromes; for 7 items, 15 diallels mediate 31 diadromes; and so on. Thus, from simple topological considerations, it is clear that if d be the number of diallels and D, the number of diadromes, and if the diallels be arranged in such a manner as to produce the maximum possible number of diadromes, then $D = 2^{-1/2+\sqrt{1/4+2d}} - 1$. For an astronomically large number of diallels $D \rightarrow 2^{\sqrt{2d}}$, but d is less than 10^{10}. Therefore, D, is less than 10^{42000}.

This investigation has been aided by a grant from the Josiah Macy, Jr. Foundation.

LITERATURE

McCulloch, W. S. and W. Pitts. 1943. "A Logical Calculus of the Ideas Immanent in Nervous Activity." *Bull. Math. Biophysics*, 5, 115-133.

BULLETIN OF
MATHEMATICAL BIOPHYSICS
VOLUME 7, 1945

ERRATA

In the paper "On the Theory of Blood-Tissue Exchanges: I. Fundamental Equations" by R. E. Smith and M. F. Morales, Volume 6, pp. 125-131, on page 129 the expression ω_j should read:

$$\frac{1}{V_0 + \sum_{i=1}^{i=n} \alpha_i h^2_i V_i \left(\frac{S_i}{V_i} \right)^2 \Delta^{-2}_{ij}},$$

and not $$\frac{1}{V_0 + \sum_{i=1}^{i=n} \alpha_i h_i V_i \left(\frac{S_i}{V_i} \right)^2 \Delta^{-2}_{ij}}.$$

The right-hand member of equation (12) should be

$$\omega_j k_j V_s \left(\frac{S_s}{V_s} \right)^2 h^2_s \Delta^{-2}_{sj} > 0, \text{ and not } \omega_j k_j V_s \left(\frac{S_s}{V_s} \right)^2 > 0.$$

The right-hand member of equation (14) should be

$$-\omega_j k_j h^2_s \left(\frac{S_s}{V_s} \right)^2 \Delta^{-2}_{sj} \alpha_s, \text{ and not } -\omega_j k_j h^2_s \left(\frac{S_s}{V_s} \right)^2 \Delta^{-2}_{sj}.$$

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BOOK REVIEW

ALSTON S. HOUSEHOLDER AND HERBERT D. LANDAHL. *Mathematical Biophysics of the Central Nervous System* (Mathematical Biophysics Monograph Series, No. 1). 1945. ix + 124 pp. Bloomington, Indiana: The Principia Press. $2.00.

The readers of this journal will welcome this monograph which systematizes and elaborates most of the work done since 1938 by A. S. Householder, H. D. Landahl, N. Rashevsky, W. Pitts, and others on the mathematical biophysics of psychological processes. The authors have undertaken the difficult task of writing about a rapidly growing research field. They realize their position but conclude that the value of a comprehensive treatment at this time to theorists and experimenters interested in contributing to the development of this subject far outweighs the risk of their treatment becoming rapidly dated.

Following a brief preface, the authors in the introduction set forth the threefold development of the work: first, an idealized neural model; second, an investigation of the properties of certain neural complexes; third, comparison of predictions with experiment:

In Part I, p. 1 to p. 36, with Chapters

I. Trans-synaptic Dynamics
II. Chains of Neurons in Steady-State Activity
III. Parallel, Interconnected Neurons
IV. The Dynamics of Simple Circuits
V. The General Neural Net

the theoretical structure is elaborated from the two-factor dynamical model of Rashevsky. From plausible assumptions, they deduce testable conclusions which check the appositeness of the simple model as an approximation to certain actual neural mechanisms.

In Part II, p. 37 to p. 102, with Chapters

VI. Single Synapse: Two Neurons
VII. Single Synapse: Several Neurons
VIII. Fluctuations of the Threshold
IX. Psychological Discrimination
X. Multidimensional Psychophysical Analysis
XI. Conditioning
XII. A Theory of Color-Vision
XIII. Some Aspects of Stereopsis

the authors follow two paths in testing their conclusions: they examine specific neural structures seeking to determine for each the response as a function of the stimulus, while in the final chapters they start with a function and construct a mechanism. The comparisons with experiment are uniformly good. Although this section is primarily concerned with applications, a great deal of the material of Chapter XI and most of Chapters X, XII, and XIII is theoretical.

The reviewer believes that a careful reading of this part especially would go far in convincing the most skeptical psychologist of the efficacy of this technique in his field. And from that viewpoint, the monograph as a whole is more impressive evidence "that mathematics, even *in a relatively fundamental sense,* will from time to time be of use to biology" (Harris, Reginald G. 1935. "Mathematics in Biology." *The Scientific Monthly,* 40, 504-510). (Italics mine.)

In Part III, p. 103 to p. 113, with Chapters

XIV. The Boolean Algebra of Neural Nets
XV. A Statistical Interpretation

the authors shift from a macroscopic time scale to the microscopic in the use of a time unit of the order of a millisecond. The treatment follows the work of W. S. McCulloch and W. Pitts who employed some of the concepts of Boolean Algebra to give a formalized picture of neural activity. Their technique is used to construct a net capable of giving the sensation of heat produced by transient cooling. In Chapter XIV, they present the work of H. D. Landahl, W. S. McCulloch, and W. Pitts which enables one to translate from the microscopic theory to the macroscopic.

The concluding chapter has one of the clearest statements of a basic tenet of such theoretical developments that this reviewer has seen:

> "The advantage of having a theory lies not only in the fact that the theory, if it should prove accurate in its predictions, provides just that much of an increase to our fund of knowledge, or increases by just that much our command over nature. A well-formulated theory, in addition, gives direction and meaning to experimental work even when the experiments fail to confirm the theory, since the failure must occur in a certain direction, by a certain amount, and must therefore provide the necessary, hitherto lacking, background for the construction of a better theory."

The monograph requires little mathematical knowledge beyond the elements of differential equations, and, for Part III, some knowledge of symbolic logic. The reviewer believes that a short appendix on Boolean Algebra would have been of value to psychologists and others who know the calculus but who may be repelled by this strange sounding mathematics! The reviewer observed only one unimportant typographical error. There is a bibliography and an excellent index. The format and typography are excellent even when judged by pre-war standards.

This monograph is a worthy and important addition to the growing literature of mathematical biophysics. It should be of inestimable aid to psychologists and neurologists seeking a fresh, stimulating vantage point from which to view their subjects. The reviewer believes that a more auspicious inauguration of a research series would be difficult to find.

HERMAN BRANSON
Department of Physics
Howard University

SCOPE OF THE BULLETIN

1. The Bulletin is devoted to publications of research in Mathematical Biophysics, as contributing to the physicomathematical foundations of biology in their most general scope.

2. Papers published in the Bulletin cover physicomathematical theories as well as any other mathematical treatments of biological phenomena, with the exception of purely statistical studies.

3. Mathematical studies in physics or in borderline fields in which a direct connection with biological problems is pointed out are also accepted.

4. Emphasis is put upon the mathematical developments, but a description and discussion of experimental work falls also within the scope of the Bulletin provided that description or discussion is made in close connection with mathematical developments *contained in the same paper.*

5. Outside of the scope of the journal are papers of purely statistical nature or papers concerned only with empirical equations.

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All manuscripts should be typewritten double space with margins $1\frac{1}{2}''$ on top, bottom and sides. Equations should be numbered on the right consecutively. *Do not* use such notations as "equation 2a" or, "equation 5′ " etc. References should be all given at the end of the paper, arranged in alphabetic order by authors and for each author chronologically, following *exactly* the style used in the Bulletin. In text, reference should be made by giving in parentheses the name of the author followed by the year of publication. In case of several publications by the same author in the same year, use notations "1940a", "1940b", etc.

In writing equations, slanted lines should be used wherever possible.

Every paper is to be preceded by a short abstract.

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